20/Declaration 1.132 + Prior Art w/att

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Patent Application of Douglas E. Kligman, *et al.*	: Group Art Unit 1615
Appln. No:	09/131,076	: Examiner: Susan Tran
Filed:	August 7, 1998	:
Title:	COMPOSITION AND METHOD OF EFFECTING SUPERFICIAL CHEMICAL SKIN PEELS	: Attorney Docket : No. **10052-1U1**

DECLARATION OF DOUGLAS E. KLIGMAN, M.D., PH.D. UNDER 37 C.F.R. §1.132

I, Douglas E. Kligman, declare and state as follows:

1. I am the same Douglas E. Kligman who is an inventor and applicant in the above-identified patent application. I am also the same Douglas E. Kligman who made a Declaration in response to the Written Opinion in counterpart International Application PCT/US97/01919, a copy of which Declaration was submitted in the above application with the Amendment dated January 26, 2000.

2. I make this Declaration in response to the Office Action dated October 3, 2000 (Paper No. 14), and more particularly to verify and supplement the statements made by me at the interview with Examiners Tran and Kishore at the U.S. Patent and Trademark Office on February 15, 2001.

Prior Art Relied Upon by Examiners

3. At the interview it was pointed out that the two prior art references relied

upon by the Examiner in the outstanding Office Action use very low amounts of salicylic acid. Thus, U.S. Patent 4,318,907 of Kligman et al. teaches the use of about 3% to about 7% by weight, and preferably about 5% by weight, of salicylic acid. In fact, Kligman '907 teaches against the use of as much as 10% salicylic acid with 5% benzoyl peroxide, because of excessive redness and peeling (see column 2, lines 44-62). Similarly, U.S. Patent 5,730,991 of Rapaport teaches the use of about 0.1% to about 5% salicylic acid in various combination peeling/exfoliating agents (see columns 14 and 15, particularly the Tables, of Rapaport). In contrast, the presently claimed invention specifies a solution containing at least 15 weight % salicylic acid.

4. Examiner Kishore argued at the interview that salicylic acid is a known exfoliating agent, and there are known acids which have been used in the prior art at high concentration to produce a chemical peel. Therefore, he asked, in light of the teachings of Kligman '907 and Rapaport to avoid higher concentrations which produce redness, what is unexpected about increasing the concentration of salicylic acid to produce a chemical peel? Examiner Kishore also argued that penetration is affected by the vehicle for the acid.

Summary of Chemical Skin Peels

5. I then gave a brief history of chemical skin peels and showed the Examiners a copy of the book by Mark G. Rubin, *Manual Of Chemical Peels-Superficial And Medium Depth*, J.B. Lippincott Company, Philadelphia (1995), portions of which had already been submitted with the Information Disclosure Statement filed with this application. At the request of the Examiners, copies of Chapters 2 and 7 (entitled "What Are Skin Peels?" and "Glycolic Acid Peels," respectively) are being provided with this Declaration and response to the Office Action.

6. Currently, in addition to the solutions of the present invention, superficial skin peeling agents include trichloroacetic acid (15-30%), alpha-hydroxy acids (e.g., glycolic acid, 40-70%) and Jessner's solution (14% lactic acid, 14% resorcinol and 14% salicylic acid). Dermatologists skilled in the art previously thought that salicylic acid was not a strong enough acid to be used alone as a skin peeling agent, and there was also the fear of salicylism, even using the 14% salicylic acid of Jessner's solution. Swinehart came along with a high concentration paste of salicylic acid for use on the forearms which requires the use of an occlusive dressing over a period of 48 hours (see discussion at bottom of page 3 of the present application and the Swinehart article cited therein and of record in the present application). Such a treatment is inconvenient and would be unacceptable to most people, particularly on the face. The chemical peel composition and method of the present invention were developed to avoid some of the disadvantages of these prior art treatments, and resulted in a number of unexpected results as discussed more fully below.

Comparison of Salicylic Acid with Glycolic Acid Peels

7. Examiner Kishore asked about comparative data with other skin peels. We have done many other superficial chemical skin peels and have compared the high concentration salicylic acid solutions of the present invention to high concentration glycolic acid, among others. Glycolic acid is currently the most popular agent for superficial chemical peels of facial skin. Glycolic acid is typically used at a concentration of 40 to 70% for chemical peeling. When applied to human skin, the reaction needs to be stopped by neutralization of the glycolic acid, usually several minutes after application. The longer the glycolic acid remains on the skin, the greater the penetration, even into the dermis. Therefore, glycolic acid can be used at high concentration for deeper chemical peeling. A disadvantage is that one sees epidermal necrosis

(dying off of epidermal cells and tissue).

8. Both salicylic acid and glycolic acid have a similar pKa, approximately 3, so that the deep chemical peeling by glycolic acid is not simply a matter of acidity. Instead, it appears to relate to the structure of the molecules. Structurally, salicylic acid is a derivative of phenol and is therefore aromatic and lipophilic. In contrast, alpha-hydroxy acids, such as lactic acid and glycolic acid, are hydrophilic. Hence, their pathway through the stratum corneum barrier is quite different from a lipophilic molecule.

9. When used alone below about 15 wt % concentration, salicylic acid does not cause enough peeling and desquamation to have a very significant clinical benefit as a superficial chemical peel. As a practical matter, salicylic acid is soluble in organic volatile solvents up to only about 30%. The peels according to the present invention use salicylic acid in solution approaching its saturation point in organic solvents, preferably lower alkyl alcohol solvents, that are volatile in air. With the solution and treatment of the present invention, the chemical peel does not have to be timed. The solution is simply applied to the skin, and upon exposure to air, the salicylic acid begins to crystallize, which takes approximately two and one-half to three minutes. At that point in time, the solvent has evaporated, and there is no further penetration of the salicylic acid into the skin. The crystalline salicylic acid is then simply washed off the patient's skin. In contrast, peeling with alpha-hydroxy acids, such as glycolic acid, needs to be timed and neutralized to stop the penetration.

10. Attached hereto are two photographs of histological (H & E) slides, one taken two days after a 70% glycolic acid peel application and the other two days after a 30% salicylic acid peel application. We see on histology (bottom slide) that salicylic acid causes stratum corneum dissolution and perhaps a small amount of damage to the stratum granulosum.

However, the deeper suprabasalar, stratum spinosum and basal layers (stratum basale) are spared. As can be seen on histology (top slide) of the glycolic acid peel, in which the glycolic acid was left on facial skin for three to four minutes, there is vacuolization (white or light areas) and necrosis (dark spots) of keratinocytes in the basal layer.

11. It is known that the stratum corneum is a barrier to transepidermal water loss, and that there is a homeostatic mechanism, such that if the stratum corneum is removed, a burst of mitosis (cell division) is instituted in the basal layer so as to regenerate the stratum corneum. This homeostatic mechanism is probably the mechanism of improvement in the epidermal layer of skin after chemical peeling with salicylic acid. Given the lack of deep penetration with salicylic acid, a wide margin of safety is allowed, which represents a significant advance over alpha-hydroxy (e.g., glycolic) acid superficial chemical peeling.

12. Histology after glycolic acid peeling also shows significant perivascular inflammatory infiltrates in the dermis, whereas very minimal inflammatory response is seen after salicylic acid peeling. Additionally, salicylic acid may have some anti-inflammatory properties itself with regard to inhibition of prostaglandin synthesis. For example, we have seen rapid improvement of inflammatory acne when treated with salicylic acid peeling (see Paragraph 14 below).

13. Further, results and discussion of a comparison between salicylic acid peels and glycolic acid peels for treatment of photoaging appear in the attached reprint of Kligman et al., "Salicylic Acid Peels For The Treatment Of Photoaging," *Dermatological Surgery*, 24: 325-328 (1998). As noted in item number 4 at page 326, 30% salicylic acid caused significantly more desquamation than 70% glycolic acid, leading to more rapid smoothing and greater efficacy of the superficial peeling agent. Hence, as noted above, the efficacy of the peel

is not simply a matter of the acidity of the peeling agent, the length of time of the peel or the penetration due to solvent. Note also the commentary of another dermatologist which appears at the bottom of page 328 of this article, which further demonstrates a recognition in the art of the unexpected benefits of salicylic acid peels according to the present invention.

Other Literature Reports of Salicylic Acid Peels

14. Enclosed is a copy of an article which I co-authored, Kligman et al., "Salicylic Acid As A Peeling Agent For The Treatment Of Acne," *Cosmetic Dermatology*, 10: 44-47 (September 1997), reporting the use of a 30% salicylic acid solution in 95% ethanol for effecting superficial chemical peeling in the treatment of various forms of acne. Note particularly the confirmation of the special advantages of the present invention in the Conclusion section beginning at the bottom of the right hand column on page 46 of the article.

15. Also enclosed is a copy of the article of Pearl E. Grimes, "The Safety And Efficacy Of Salicylic Acid Chemical Peels In Darker Racial-Ethnic Groups," *Dermatological Surgery*, 25: 18-22 (1999). This article demonstrates the safe and efficacious skin peeling of certain skin types in the treatment of acne vulgaris and other skin conditions using 20% and 30% salicylic acid peels according to the present invention. Prior to this invention, many dermatologists were reluctant to perform peels on persons with these skin types because of the risk of hyperpigmentation or hypopigmentation. This is a further unexpected benefit of the present invention.

16. There is further enclosed a copy of an article S. Imayama et al., "Histologic Changes In The Skin Of Hairless Mice Following Peeling With Salicylic Acid," *Archives Of Dermatology*, 136: 1390-1395 (November 2000), reporting studies of applying various concentrations of salicylic acid in ethanol or macrogol solution to the backs of hairless

mice. The study evaluates the changes in the skin 48 hours ~~after the application of salicylic acid~~ solutions. Hairless mice were used because they have been previously used to study experimental aging. Note the conclusion that the architecture of the epidermis and papillary dermis can be regenerated by injuring the cornified layer using topical salicylic acid which does not cause degeneration or inflammation.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that those statements were made with the knowledge that willful false statements the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: May 7, 2001 Douglas E. Kligman

DOUGLAS E. KLIGMAN, M.D., PH.D.

Attachments